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(54) Title: PREPARATION OF (THREO)-1-ARYL-2-ACYLAMIDO-3-FLUORO-1-PROPANOLS

(57) Abstract

A novel sequence of highly selective chemical reactions for conversion of 3-Aryl-2-propyn-1-ols into *cis*-1-Aryl-3-fluoro-1-propene and into D,L-(threo)-1-Aryl-2-acylamido-3-fluoro-1-propanols. Preparation of D-(threo)-1-Aryl-2-acylamido-3-fluoro-1-propanol antibacterial agents including the D-(threo)-3-fluoro-3-deoxy derivatives of chloramphenicol and thiamphenicol.

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PREPARATION OF (THREO)-1-ARYL -2-ACYLAMIDO-3-FLUORO-1-PROPANOLS

BACKGROUND OF THE INVENTION

This invention relates to cis-1-Aryl-2-(fluoromethyl)oxiranes, and to a method of preparing such compounds.

This invention also relates to a method of preparing (threo)-1-Aryl-2-acylamido-3-fluoro-1-propanols from cis-1-Aryl-2-(fluoromethyl)oxiranes. More particularly, this invention relates to preparing D-(threo)-1-Aryl-2-acylamido-3-fluoro-1-propanol antibacterial agents, including 3-fluoro-3-deoxy derivatives of chloramphenicol and of thiamphenicol.

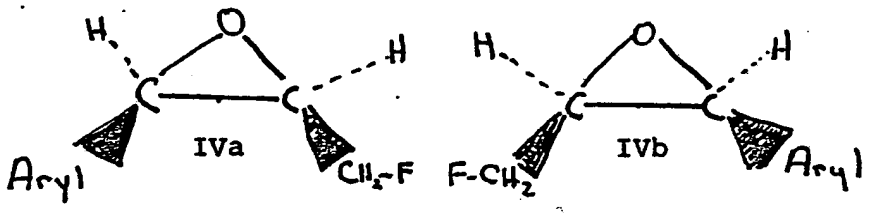
D-(threo)-1-Aryl(phenyl or para-and/or meta-substituted phenyl)-2-acylamido-3-fluoro-1-propanols and racemic mixtures thereof are known in the art as broad spectrum antibacterial agents useful in the treatment of gram positive, gram negative and rickettsial infections. See, for example, U.S. Patent No. 4,235,892, and 4,361,557.

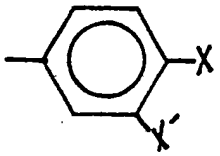
U.S. Patent No. 4,311,857 discloses methods of preparing D-(threo)-1-Aryl-2-acylamido-3-fluoro-1-

propanols by reaction of D-(threo)-1-Aryl-2-N-protected-amino-1,3-propanediol with dialkylaminosulfur trifluoride followed by removal of the N-protecting group and thence reaction of the resulting D-(threo)-1-Aryl-2-amino-3-fluoro-1-propanol with a lower alkanoic acid derivative. However, the method uses an optically active starting material and it would be economically desirable to provide a synthetic pathway to (threo)-1-Aryl-2-acylamido-3-fluoro-1-propanols employing racemic starting materials and delay a resolution of the racemic mixture to a late step in the process.

SUMMARY OF THE INVENTION

The present invention provides a process for the preparation of compounds represented by formulas IVa and IVb



wherein Aryl is  ; and wherein each of X and X' is independently NO_2, SO_2R_1, SO_2NH_2, SO_2NHR_1, OR_1, R_1,CN, halogen, hydrogen, phenyl or phenyl substituted by 1 to 3 halogens, NO_2, SO_2R_1 or OR_1; and wherein R_1 is lower alkyl; which comprises the following steps:

(a) contacting a 3-Aryl-2-propyn-1-ol with a fluorinating agent in an inert organic solvent to

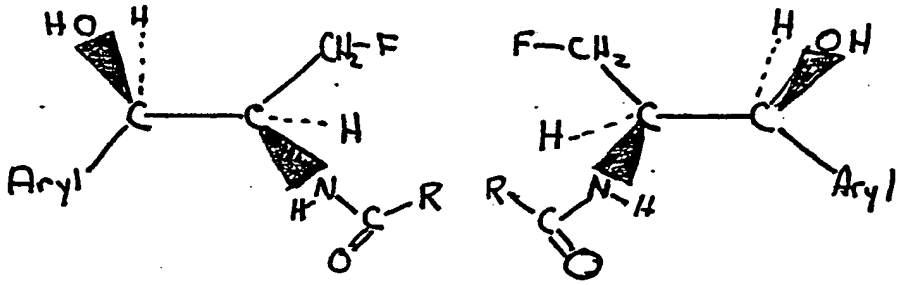
form 1-Aryl-3-fluoro-1-propyne;

(b) contacting the product of step (a) with a reagent selective for cis-hydrogenation to form a cis-1-Aryl-3-fluoro-1-propene; and

(c) contacting the product of step (b) with a peroxyacid to form the compounds represented by the formulas IVa and IVb.

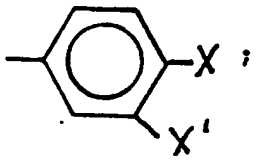
The novel compounds represented by formulas IVa and IVb are cis-1-Aryl-2-(fluoromethyl)oxiranes, useful as intermediates in the preparation of D,L-(threo)-1-Aryl-2-acylamido-3-fluoro-1-propanols.

The present invention also provides a process for the preparation of D,L-(threo)-1-Aryl-2-acylamido-3-fluoro-1-propanols represented by formulas VIa and VIb



VIa VIb

wherein R is lower alkyl or a halogenated derivative thereof; dihalogenodeuteriomethyl, 1-halogeno-1-deuterioethyl; 1-2-dihalogeno-1-deuterioethyl; azidomethyl; or methylsulfonylmethyl; wherein Aryl is



wherein each of X and X' is independently NO_2, SO_2R_1, SO_2NH_2, SO_2NHR_1, OR_1, R_1, CN, halogen, hydrogen, phenyl, or phenyl substituted by 1-3 halogens, NO_2, SO_2R_1, R_1, or OR_1; and wherein R_1 is lower alkyl which comprises the following steps:

(1) converting a cis-1-Aryl-2-(fluoromethyl)oxirane into D,L-(threo)-1-Aryl-2-amino-3-fluoro-1-propanol either by (i) contacting the cis-1-Aryl-2-(fluoromethyl)oxirane with an alkali metal azide to form D,L-(threo-1-Aryl-2-azido-3-fluoro-1-propanol and then reducing the 2-azido group to a 2-amino group or (ii) contacting the cis-1-Aryl-2-(fluoromethyl)oxaine with an imido compound to form a D,L-(threo)-1-Aryl-2-imido-3-fluoro-1-propanol and then converting the 2-imido group to a 2-amino group thereby forming D,L-(threo)-1-Aryl-2-amino-3-fluoro-1-propanols;

(2) contacting the product of step (1) with a lower alkanoic acid derivative selected from lower alkyl alkanoic acid anhydrides, lower alkyl alkanoyl halide, or a halogeno lower alkyl alkanoic acid halide or anhydride in the presence of a base, or a lower alkyl ester of an α,α-dihalogeno acetic acid or an α,α-dihalogeno propionic acid in a lower alkyl alkanol to produce the compounds of formulas VIa and VIb; and

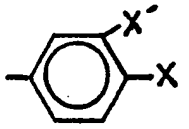
(3) recovering compounds of formulas VIa and VIb.

In a preferred embodiment of the present invention the racemic mixture of D,L-(threo)1-Aryl-2-amino-3-fluoro-1-propanols, obtained from step (1) of the process is resolved by fractional crystallization of a diastereomeric salt of D-(threo)-1-Aryl-2-amino-3-fluoro-1-propanol and an optically active acid followed by treatment of the diasteriomeric salt with aqueous base and recovery of D-(threo)-1-Aryl-2-amino-3-fluoro-1-propanol, and thence treatment of the D-threo compound with a lower alkanoic acid derivative to form the D-threo enantiomer of the compound of formula VIa.

DETAILED DESCRIPTION OF THE INVENTION

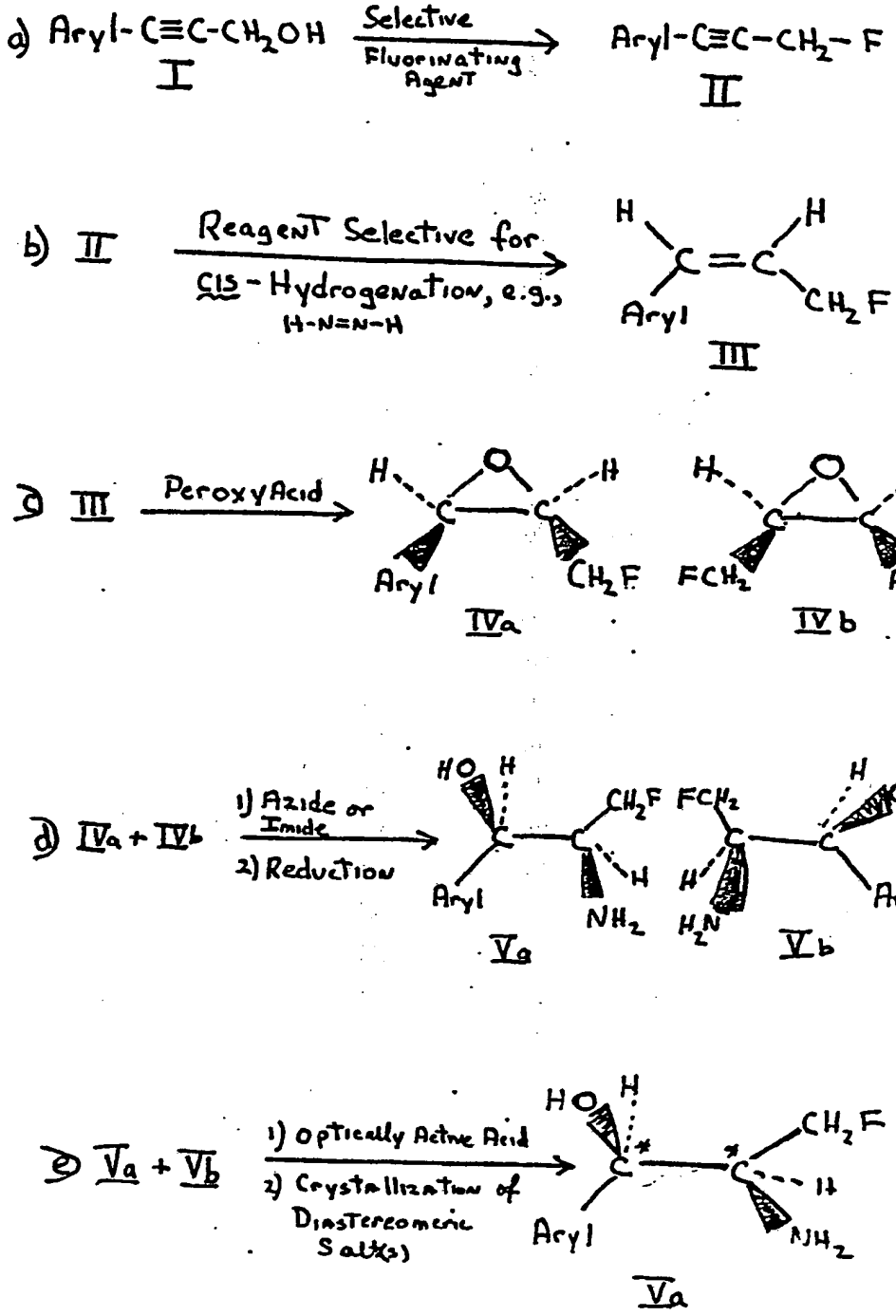
The term "halogen" as used herein means fluorine, chlorine, bromine or iodine. Fluorine and chlorine are preferred.

The term "lower alkyl" as used herein means straight or branched (C_1-C_6) alkyl including methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, tert-butyl, n-pentyl, iso-pentyl, neo-pentyl, n-hexyl, iso-hexyl. Methyl and ethyl are preferred.

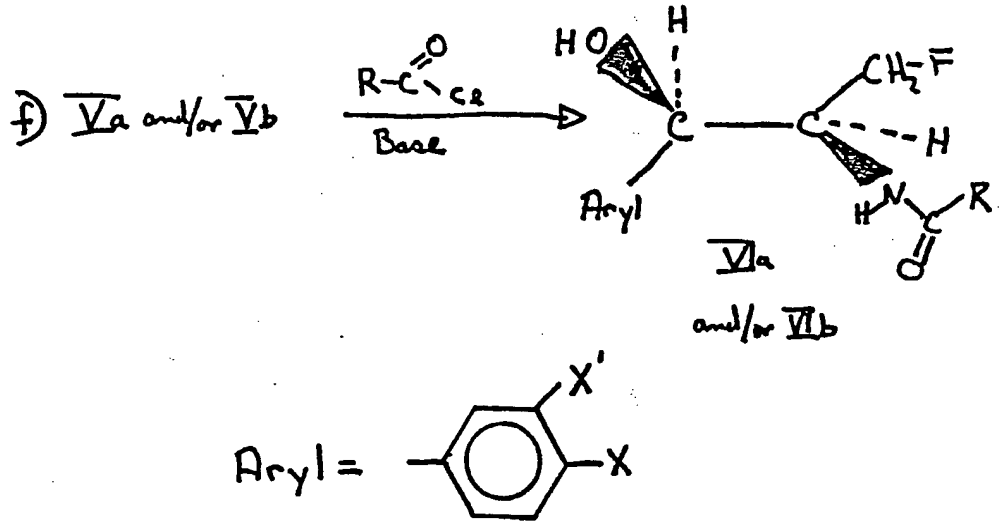
The term "Aryl" as used herein means phenyl or 4-substituted or 3,4-disubstituted phenyl represented by formula  wherein each of X and X' is a member selected from the group consisting of NO_2, SO_2R_1, SO_2NH_2 SO_2NHR_1, OR_1, R_1, CN, halogen, hydrogen, phenyl and phenyl substituted by halogen, NO_2, SO_2CH_3 R_1 or OR_1 and wherein R_1 is methyl, ethyl, propyl or isopropyl and wherein halogen is fluorine, chlorine or bromine. Particularly interesting Aryl groups are 4-nitrophenyl (X is NO_2) and 4-methylsulfonylphenyl (X is SO_2CH_3) and 4-sulfonamidophenyl (X=SO_2NH_2).

The following Scheme illustrates the multistep processes of this invention for preparing cis-1-Aryl (phenyl or para- and/or meta-substituted phenyl)-(2-fluoromethyl)oxiranes and for preparing D,L-(threo) and D-(threo)-1-Aryl(phenyl or para and/or meta substituted phenyl)-2-acylamido-3-fluoro-1-propanols. The processes comprise a novel sequence of highly selective chemical reactions.

SCHEME

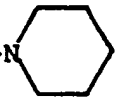
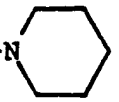

a) Aryl-C≡C-CH2OH
I
Selective
Fluorinating
Agent
Aryl-C≡C-CH2-F
II
b) II
Reagent Selective for
cis-Hydrogenation, e.g.,
H-N=N-H
H
H
Aryl
CH2F
III
c) III
Peroxy Acid
H
O
H
Aryl
CH2F
IVa
FCH2
Aryl
IVb
d) IVa + IVb
1) Azide or
Imide
2) Reduction
HO
H
CH2F
Aryl
H
NH2
Va
FCH2
H
OH
H
H2N
Aryl
Vb
e) Va + Vb
1) Optically Active Acid
2) Crystallization of
Diastereomeric
Salt(s)
HO
H
CH2F
Aryl
H
NH2
Va

SCHEME (Cont'd.)

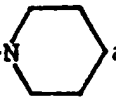


The 3-Aryl-2-propyn-1-ols represented by formula I used as starting materials in step (a) of the processes of the present invention are either known compounds or are conveniently prepared according to known procedures. For example, 3-(4-methylsulfonylphenyl)-2-propyn-1-ol is conveniently prepared by reacting 4-bromophenyl methyl sulfone with propargyl alcohol in the presence of copper(I)iodide bis(triphenylphosphine) palladium(II)chloride and triethylamine. A general experimental procedure for preparation of 3-Aryl(phenyl or para and/or meta substituted phenyl)-2-propyn-1-ols, such as 3-(4-nitrophenyl)-2-propyn-1-ol is described by M.A. Harris et al. in J. Chem. Soc, Perkin I, pages 1612-1613 (1976).

In step a) of the process depicted in the reaction Scheme, the primary hydroxy moiety in 3-Aryl-2-propyn-1-ol (compound I) is selectively converted into the corresponding primary fluoro moiety (compound 2). Suitable selective fluorinating agents include compounds with two fluorine atoms α to a nitrogen, for example

$CHClFCF_2N(C_2H_5)_2$ or $CHCF_3$-  or HCF_2-  and

compounds having a flourine atom attached to a hetero atom (e.g. S or P) such as SOF_2, PF_5, SF_4, F_3S-$N(C_2H_5)_2$,

F_3S-  and $(C_6H_5)_3PF_2$. The preferred

fluorinating agent is N-(1,1,2-trifluoro-2-chloroethyl)-N,N-diethylamine, $CHClFCF_2N(C_2H_5)_2$.

The fluorinating step is conveniently carried out at temperatures in the range of about -10° to about + 50°C, preferably about 0 - 30°C in an inert organic solvent. The term "inert organic solvent" means any organic solvent in which compound I and the fluorinating reagents are soluble, and which is essentially inert under the reaction conditions. Dichloromethane is especially preferred.

In step b) of the process depicted in the reaction Scheme, the 1-Aryl-3-fluoro-1-propyne represented by formula II is reduced to the cis-1-Aryl-3-fluoro-1-propene represented by formula III by use of a reagent selective for cis-hydrogenation such as dimide or hydrogen with a Lindlar catalyst, i.e., palladium precipitated on calcium carbonate and lead (II) oxide selectively poisoned by an aromatic amine, such as quinoline or pyridine in an organic solvent, e.g., ethyl acetate that dissolves at least compound II. Other reagents selective for cis-hydrogenation in the process of the present invention include a palladium-on-barium sulfate catalyst poisoned by synthetic quinoline [See D.J. Cram et al., J. Am. Chem. Soc., 78, 2518 (1956)] or 5% palladium-on-barium sulfate used with pyridine as a solvent [see "Feiser and Feiser's Reagents for Organic Synthesis", Vol. 2, pages 566-569) (1969)]. The

particular reagent chosen will depend upon the substituents on the phenyl ring and solubility of the compound represented by formula II as well as the ability of the reagent to effect selective cis-hydrogenation of the triple bond with a minimum of side reactions. For the selective cis-reduction of the triple bond of 1-(4-methylsulfonylphenyl)-3-fluoro-1-propyne, hydrogen and the Lindlar catalyst selectively poisoned with quinoline are preferred (see H. Lindlar et al. Org. Syn., 46, 89 (1966)); for the selective cis-reduction of the triple bond of 1-(4-nitrophenyl)-3-fluoro-1-propyne, dimide is preferred (see "Fieser and Fieser's Reagents for organic Synthesis", Vol. 8, page 172, Wiley-Interscience, N.Y. 1980). Reaction conditions are not critical; generally, hydrogen pressures of about 1 atmosphere, room temperature and 1-24 hrs. are used.

In step c) of the process depicted in the reaction Scheme, the cis-1-Aryl-3-fluoro-1-propene (compound III) is converted into the cis-1-Aryl-2-(fluoromethyl)oxiranes (compounds IVa and IVb) by use of an aliphatic or aromatic peroxyacid. Among the suitable aromatic peroxyacids are m-chloroperbenzoic acid, perbenzoic acid, and peroxyphthalic acid. Among the suitable aliphatic peroxyacid acids are peracetic acid and trifluoroperacetic acid. The preferred peroxyacid for step c) is m-chloroperbenzoic acid. Reaction conditions are not critical. Chlorinated solvents, e.g., dichloromethane, reflux temperatures, and reaction times of 10-30 hrs are typically used. See "Feiser and Feiser's Reagents for Organic Synthesis", Vol. 9. pages 108-110.

Compounds IVa and IVb formed in step c are novel compositions of matter and isolated and purified by standard techniques, e.g. extraction, filtration, chromatography and crystallization. The term "Aryl" in

cis-1-Aryl-2-(fluoromethyl)oxirane is defined hereinabove. Particularly interesting compounds represented by formulas IVa and IVb are cis-1-(4-nitrophenyl)-2-(fluoromethyl)oxirane, cis-1-(4--sulfonamidophenyl-2-(fluoromethyl)oxirane.

When compounds IVa and IVb are used to produce the D,L- or D-(threo)-1-Aryl-2-acylamido-3-fluoro-1-propanols, process steps d + f or d + e + f are performed, respectively. Generally, it is desirable to isolate and purify compounds IVa and IVb after step (c) is performed.

In step d) of the process depicted in the reaction Scheme, the cis-1-Aryl-2-(fluoromethyl)oxiranes (compounds IVa and IVb) are selectively converted into a racemic mixture of D,L-(threo)-1-Aryl-2-amino-3-fluoro-1-propanols (compounds Va and Vb) by use of nucleophilic nitrogen compounds in a dry aprotic solvent such as dimethylformamide or dimethyl sulfoxide at elevated temperatures (90°-120°C) for 10-40 hrs. Typical suitable nucleophilic nitrogen compounds are alkali metal (especially Na^+ and K^+) imides .e.g., potassium salts of phthalimide, 1,8-naphthalene dicarboximide, 5,6-norbornene dicarboximide or succinimide in combination with the free imide in a ratio of 1:4 to 0.05:4. The aroyl group, e.g., phthaloyl group is conveniently removed by treatment with hydroxylamine hydrochloride and an alkoxide base, e.g., sodium methoxide in methanol to produce the free amine. Other suitable nucleophilic nitrogen compounds include the alkali metal azides (e.g., NaN_3, KN_3) preferrably buffered with, for example, ammonium chloride. The azido group is reduced, conveniently with hydrogen in the presence of a catalyst, especially with hydrogen and 10% palladuim-on-charcoal at atmospheric pressure and at room temperature to give compound Va and Vb containing the free amino group. Use

of either alkali metal azides or alkali metal imido compounds in combination with the free imide produces a mixture of compounds which must be purified by, for example, fractional crystallization before conversion to the free amine is effected.

In step f) of the process depicted in the reaction Scheme, D,L- or D-(threo)-1-Aryl-2-amimo-3-fluoro-1-propanols (the mixture of compounds Va and/or Vb) is converted into the 2-acylamido derivative compounds VIa and VIb by reaction of compounds Va and/or Vb in the presence of a base and a suitable organic solvent for the reactants with a lower alkyl alkanoic acid derivative or a halogeno lower alkyl alkanoic acid halide (e.g. fluoride, chloride) or anhydride, or with a lower alkyl ester of an α,α-dihalogeno-propionic acid under reflux until the reaction goes to completion, typically in 10-20 hrs. Halogeno acetic or propionic acid chlorides are preferred halogeno lower alkyl alkanoic acid halides. Typically, the base is an aliphatic amine and the organic solvent suitable for the reactants is a lower alkyl alkanol, especially methanol or ethanol or a halogenated alkane, e.g. dichloromethane. Of the lower alkyl alkanoic acid derivatives, acetic and propionic acid, chlorides and acid anhydrides are preferred. Of the lower alkyl esters of the preferred acid derivatives, the methyl and ethyl esters of the dihalogeno acetic acids and the α,α-dihalogenopropionic acids are preferred. Typical of the lower alkyl halogeno alkanoic acid derivatives are halogeno acetic and halogeno propionic acid chlorides or anhydrides, especially those substituted by one, two or three halogens (F, Cl, Br or I) including mono-,di-and trifluoro-, mono-,di-and trichloro- and mono-and dibromo- and mono-iodoacetic acid chlorides or anhydrides or esters as well as the mono-and difluoro-, the mono-and

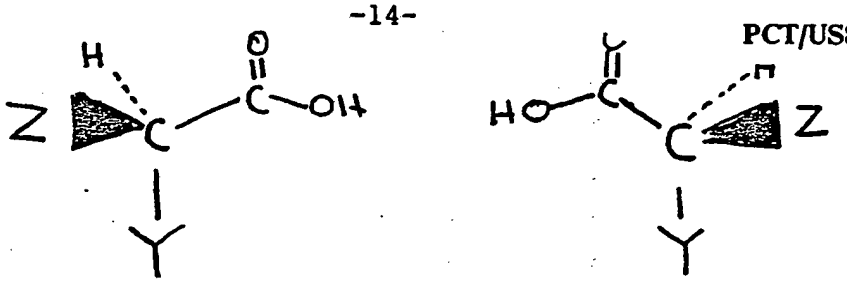
dichloro-, the mono- and dibromo- and the mono-iodiopropionic acid chlorides or anhydrides or esters. The halogen substituents in the propionic acid derivatives are preferably on the carbon alpha to the carbonyl function. Other typical suitable alkanoic acid derivatives are the mixed dihalogeno acetic and dihalogeno propionic acid derivatives in which both halogens are preferably bonded to the carbon alpha to the carbonyl function, e.g., fluorochloro-, fluorobromo- and chlorobromoacetic acid chlorides or anhydrides or esters as well as α-fluoro-, α-chloro- and α-bromopropionic acid chlorides or anhydrides or esters as well as trihalogeno-acetic acid derivates such as dichlorofluoro- and difluorochloroacetic acid chlorides or anhydrides or esters. Additionally, suitable are those halogeno acetic and halogeno propionic acid chlorides and anhydrides and esters having a deuterio atom on the carbon alpha to the carbonyl function, e.g. dihalogenodeuterioacetic acid chlorides or anhydrides such as dichlorodeuterio difluorodeuterio- and chlorofluorodeuterioacetic acid chlorides or anhydrides or esters, as well as α,α-difluoro-α-deuterio-,α-fluoro-α-deuterio- and α,α-dichloro-α-deuteriopropionic acid chlorides, anhydrides or esters. Of the foregoing, dichloroacetic, difluoro-acetic, fluorochloroacetic acid chlorides, anhydrides and the methyl and ethyl esters as well as deuterio derivatives thereof are preferred.

The racemic mixture of compounds Va and Vb resulting from step d) of Scheme detailed above has antifungal activity. However, the preferred biologically active D-(threo)-enantiomer, compound Va, can be separated from the racemic mixture by a variety of techniques known to those skilled in the art, but preferably by fractional crystallization of the diastereomeric ammonium carboxylate salt of the D-(threo)

enantiomer with an optically active acid.

The resolution step of the preferred embodiment of the process of the present invention is performed on the racemic mixture of D,L-(threo)-1-Aryl-1-2-amino-3-fluoro-1-propanols (compounds Va and Vb) prior to the step f) of the process depicted in the reaction Scheme. The racemic mixture of compounds represented by formulas Va and Vb is contacted with an optically active acid, one enantiomer of which forms a crystalline diasteromeric salt with the D-(threo)-1-Aryl-2-amino-3-fluoro-1-propanol (compound Va), said salt having a higher melting point, and/or a lower solubility and/or higher crystallizability compared to that for the L-threo enantiomer. As is well known to those skilled in the art, it is advantageous to explore, on a millimole scale, the salt forming properties i.e., melting point, solubilty and crystallinity of optically active acids described in the literature in order to select the optimal resolving agent available as well as to provide crystalline diasteriomeric salts which can be used as seed crystals in resolving the racemic D,L-threo aminofluoro propanol. Generally, as is well known in the art, a resolution through separation by crystallization of diasteriomeric salts is most likely to succeed without difficulty when the acid and basic salt-forming centers of both components are proximate in space to those factors which render each asymetric.

Typical suitable optically active acids useful for successful resolution of the racemic D,L-(threo)-1-Aryl-2-amino-3-fluoro-1-propanols are those acids represented by the formulas A and B



A B

wherein Z is a bulky alkyl or aromatic group such as phenyl, napthtyl, (C_4-C_{10}) branched alkyl (e.g. isobutyl, neopentyl, isohexyl, isooctyl and the like) and wherein Y is a polar group such as $-OR_2$, $NH-\overset{O}{\overset{\|}{C}}-R_2$ or $O-\overset{O}{\overset{\|}{C}}R_2$ or $O-\overset{O}{\overset{\|}{C}}-Ar$ wherein R_2 is straight or branched (C_1-C_6)alkyl, for example, methyl, ethyl, propyls, butyls, pentyls, hexyls and wherein Ar is phenyl or para- or meta-substituted phenyl. Suitable Y groups include CH_3O-, C_2H_5O-, C_4H_9O-, $C_6H_{13}O-$ $CH_3\overset{O}{\overset{\|}{C}}NH-$, $C_6H_5\overset{O}{\overset{\|}{C}}-$, $CH_3\overset{O}{\overset{\|}{C}}-O-$and $C_4H_9\overset{O}{\overset{\|}{C}}-$. O-(+)-(S)-O-methylmandelic acid (formula A wherein Y=OCH_3 and Z=C_6H_5) is especially preferred.

Generally, no more than about an equivalent of the optically active acid is heated (steam bath) with the racemic D,L-(threo)-1-Aryl-2-amino-3-fluoro-1-propanols in a suitable organic solvent. The resolution is improved by seeding of the solution of racemate and optically active acid with the authentic neutral diastereomeric salt of the desired D-(threo)-1-Aryl-2-amino-3-fluoro-1-propanol and the optimal optically active acid and thereafter stirring the mixture for a short time (2 hrs). The optical rotation and optical purities of the isolated salt and the free amine are determined and the diastereomeric salt is repeatedly recrystallized to constant optically purity. When the solution of the diastereomeric salt of D-threo-1-(4-methylsulfonylphenyl)-2-amino-3-fluoro-1-propanol (compound Va wherein Aryl = 4-$CH_3SO_2C_6H_4$-) and (+)-S-O-

methylmandelic acid was seeded with the authentic diasteriomeric salt and stirred, the isolated salt had an optical purity of about 96% and was obtained in about 46% yield after two crystallization from n-butanol.

Among the suitable organic solvents are acetone, ethanol, ethanol-ether (1:1,v/v) and n-butanol. Use of n-butanol gave the best results (higher yield and optical purity of diastereomeric salt isolated) and is preferred. The 1:1 ethanol-ether mixture gave a diastereomeric salt with an optical purity comparable to that using n-butanol, however, in lower yield.

Compound Va can be conveniently isolated as the free amine from an aqueous solution of the diastereomeric salt by treatment of the diastereomeric salt with aqueous base, e.g., alkali metal hydroxide or carbonate and extraction of Va with an immiscible organic solvent.

EXAMPLES

GENERAL EXPERIMENTAL

Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrectd. Infrared (ir) spectra were recorded with a Perkin-Elmer 598 spectrophotometer. The ^1H NMR spectra were recorded with a Bruker CXP-200 (200 MHz) or a Varian-T-60 (60 MHz) spectrometer with tetramethylsilane (TMS) as the internal standard; chemical shifts are given in parts per million down field from TMS. Optical rotations were measured with a Perkin-Elmer model 141 automatic polarimeter. Thin-layer chromatography (tlc) was performed using precoated thin-layer chromatography plates (kieselgel 60 F_{254}, E. Merck) with a fluorescence indicator in the following solvent systems (v/v): (A) ethyl acetate-hexane (1:1); (B) ethyl acetate-hexane (3:1). Compounds were located by ultraviolet light. Preparative thin-layer chromatography was performed using precoated thin-layer chromatography plates (silica gel GF, Analtech). Column chromatography was perfomed on silica gel 60 (70-230 mesh, E. Merck). Temperatures are in degrees Celsius.

EXAMPLE 1

1-(4-Methylsulfonylphenyl)-3-Fluoro-1-Propyne

To a stirred solution of N-(1,1,2-trifluoro-2-chloroethyl)-N,N-diethylamine (6.2. g 32.5 mmol) in CH_2Cl_2 (20 mL) at 0-5°, add 3-(4-methylsulfonylphenyl)-2-propyn-1-ol (4.78 g; 22.8 mmol) in CH_2Cl_2 (15 mL) over 10-15 min. Treat the solution with CF_3CO_2H (0.2 mL) and maintain the treated solution at 20-25° for 20 hrs.

Add methanol (5 mL) and partition the mixture in CH_2Cl_2-H_2O. Stir the organic phase 1hr with methanol (10 mL) and anhydrous Na_2CO_3 (10 g) [to hydrolyze any esters], filter and evaporate the organic phase. Filter the residue dissolved in CH_2Cl_2 through ~ 20 g of silica

gel and elute with CH_2Cl_2. Evaporate all product-containing-fractions and dissolve the residue

(product + $CHClFCN(C_2H_5)_2$ in ether (15 mL) and dilute the solution so formed slowly with hexanes (75 mL.). Refrigerate the solution and collect the product by filtration. Wash the filtered product with hexanes and dry the washed product at 25° in high vacuum to give fine white needles of the title compound, mp 97-99° (3.25 g ; 68% of theory).

^1H NMR ($CDCl_3$)δ:3.06 (s,3H), 5.20 (d, J=47, 2H), 7.64 (d, J=8, 2H) and 7.95 (d, J=8, 2H).

EXAMPLE 2

cis-1-(4-Methylsulfonylphenyl)-3-Fluoro-2-Propene

(A) cis-hydrogenation using Lindlar catalyst and pyridine: Stir a mixture of 533 mg, 2.51 mmoles of the title compound of Example 1 (recrystallized from dichloromethane-hexane), 211 mg, 2.67 mmoles of pyridine and 127 mg of Lindlar catalyst (palladium on calcium carbonate, poisoned with lead (obtained from Aldrich) in 25 mL of ethyl acetate under hydrogen at atomospheric pressure at 26°C for 1 hr until the theoretical amount of hydrogen (62 mL) is consumed. Remove the catalyst by filtration and wash it with ethyl acetate. Wash the ethyl acetate solution successively with ice-cold 4% HCl solution, saturated $NaHCO_3$ solution and water, and dry over anhydrous $MgSO_4$. Evaporate solvent under vacuum to give the title compound as an oil (534 mg).

(B) cis-hydrogenation using Lindlar catalyst and quinoline: Shake a mixture of recrystallized title compound of Example 1 (1 g, 4.72 mmoles), quinoline (60 mg, 99% pure Aldrich) and Lindlar catalyst of procedure A of Example 2 (200 mg) in ethyl acetate (50 mL) in a Parr

apparatus under hydrogen at atmospheric pressure at 30° for 20 min. or until theoretical amount of hydrogen (118 mL) is taken up. Remove catalyst by filtration and wash it with ethyl acetate. Evaporate the solvent under vacuum at 35° to give an oil. Dissolve the oil in dichlormethane (40 mL) and wash the dichloromethane solution successively with ice-cold 1 M HCl solution, saturated $NaHCO_3$ solution and water, and then dry over anhydrous $MgSO_4$. Evaporate the under vacuum to give the title compound as an oil (1 g). Purify a portion of the oil (220 mg) by column chromatography. Elute the column with ethyl acetate-hexane (1:1, v/v) to give the title compound as an oil (213 mg). The oil was 95% pure and contained 5% of the over-reduced compound 3-(4-methylsulfonylphenyl)-1-fluoropropane and had the following physical and spectral properties:

R_f=0.44 (solvent A); ν_{max}(film): 2990, 1580 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 3.06 (s, 3H), 5.06 (ddd, 2H, $J_{3,F}$= 46.6 Hz, $J_{3,3'}$=6.4 Hz, $J_{3,2}=J_{3',2}$=1.3 Hz), 6.06 (m, 1H, $J_{2,F}$ = 17.3 Hz, $J_{1,2}$= 12.3 Hz, $J_{2,3'}= J_{2,3}$= 1.3 Hz), 6.70 (bd, 1H, $J_{1,2}$= 12.3 Hz), 7.31 (d, 2H, J = 8.3 Hz), 7.85 (d, 2H, J=8.1 Hz).

EXAMPLE 3

cis-1-(4-Methylsulfonylphenyl)-2-(fluoromethyl)oxirane

A. Reflux a solution of the title compound of Example 2 (533 mg., 2.49 mmoles), m-chloroperbenzoic acid (m-CPBA) (863 mg., 5.00 mmoles) and 3-tert-butyl-4-hydroxy-5-methylphenylsulfide (an inhibitor, 30 mg., Aldrich) in dry dichloromethane (20 mL) (P_2O_5 dried) for 17 hrs. Add another portion of m-CPBA (400 mg.) and reflux the solution for an additional 5 hrs. Cool the solution to room temperature, and wash the cooled solution with saturated sodium bicarbonate solution (20 mL) and add thereto sodium sulfite (Na_2SO_3, 3 g.). Stir the

resulting mixture for 30 min. S parate the organic layer and extract the aqueous layer with dichloromethane (20 mL). Wash the combined organic extract with water and dry over anhydrous $MgSO_4$. Evaporate the solvent under vacuum to give a syrup. Chromatograph the syrup on two preparative tlc plates using ethyl acetate-hexane (1:1 v/v). Extract the bands containing the product with ethyl acetate to give the title compound, a solid (473 mg., 83% of theory). Recrystallized the solid from dichloromethane-ether;

m.p. 91-93°C, R_f = 0.33 (solvent A); ν_{max} (KBr): 3000, 1596 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ:3.07 (s, 3H), 3.63 (m, 1H, $J_{2,F}$ = 7.6 Hz, $J_{2,1}$ = 4.2 Hz, $J_{2,3}$ = 4.7 Hz, $J_{2,3'}$ = 6.4 Hz), 4.22 (ddd, 1H, $J_{3,F}$ = 47.5 Hz, $J_{3,3'}$ = 10.6 Hz, $J_{3,2}$ = 6.4 Hz), 4.30 (dd, 1H, $J_{1,2}$ = 4.2 Hz, $J_{1,F}$ = 2.1 Hz), 4.33 (ddd, 1H, $J_{3',F}$ = 46.8 Hz, $J_{3',3}$ = 10.6 Hz, $J_{3',2}$ = 4.7 Hz), 6.87 (d, 2H, J = 8.1 Hz), 7.96 (d, 2H, J = 8.7 Hz).

B. More conveniently, isolate the title compound (2.78 g., 68%) by direct crystallization from dichloromethane-ether of the reaction mixture from the m-CPBA peroxidation of 3.84 g of the cis-1-(4-Methylsulfonylphenyl)-3-fluoro-2-propene.

EXAMPLE 4

D,L-(threo)-1-(4-Methylsulfonylphenyl)-2-Pthalimido-3-Fluoro-1-Propanol

A. Reaction of the title compound of Example 3 with potassium phthalimide and phthalimide.

Heat a mixture of the title compound of Example 3 (500 mg., 2.17 mmoles), and finely powdered potassium phthalimide (400 mg., 2.16 mmoles) and phthalimide (1.278 g., 8.69 mmoles) in dry DMF (dried over P_2O_5 and distilled under reduced pressure) with stirring in an oil

bath under nitrogen at 93-97° for 24 hrs. Cool the reaction mixture to room temperature and pour the cooled mixture into ice-cooled 0.1 M HCl (100 mL) and extract twice with dichloromethane (30 mL). Wash the combined extract successively with saturated sodium bicarbonate (30 mL) and water and then dry over anhydrous Na_2SO_4. Evaporate the solvent under vacuum to give a solid residue, and treat the solid with ethyl acetate-hexanes (10:1, v/v). Remove the precipitated solid by filtration and wash it with ethyl acetate-hexanes (10:1, v/v) (600 mg of phthalimide). Concentrate the filtrate and remove the precipitated solid as described above. Dissolve the residue in DMSO (1 mL) and apply the solution onto a column of silica gel (100 g.). Elute the column with ethyl acetate-hexanes (3:2, v/v). Evaporate the solvent to give a solid (438 mg.), and treat the solid with isopropyl alcohol. Remove the solid by filtration and wash it with isopropyl alcohol (yield 220 mg., 26.8%). Recrystallize the compound from isopropyl alcohol to give the title compound, colorless plates, m.p. 185-187° (cf. D-(threo) isomer gave white needles from isopropyl alcohol;

m.p. 175-177°C), R_f = 0.027 (solvent B) ν_{max} (KBr): 3340 (OH), 1752 (symmetric C=O), 1685 (asymmetric C=O), 1587 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$-DMSO-d_6, 4:1, v/v)δ: 3.07 (s, 3H), 4.33 (ddd, 1H, $J_{3,F}$ = 44.9 Hz, $J_{3,3'}$ = 8.9 Hz, $J_{3,2}$ = 4.0 Hz), 4.67 (m, 1H, $J_{2,F}$ = 16.5 Hz, $J_{2,3}$ = 4.0 Hz, $J_{2,3'}$ = 8.9 Hz, $J_{2,1}$ = 8.3 Hz), 4.85 (dt, 1H, $J_{3',F}$ = 45.8 Hz, $J_{3,3'}$ = $J_{3,2}$ = 8.9 Hz), 5.30 (d, 1H, $J_{1,2}$ = 8.3 Hz), 5.83 (OH) (bs, 1H), 7.64 (d, 2H, J = 8.5 Hz), 7.76 (m, 4H), 7.88 (d, J = 8.5 Hz).

B. Reaction of the title compound of Example 3 with anhydrous potassium fluoride and phthalimide.

Stir a mixture of the title compound of Example 3 and phthalimide (364 mg., 2.48 mmoles), and anhydrous potassium fluoride (Aldrich, 556 mg.) in dry DMF (4 mL.) at 90° in an oil bath for 35 hrs. Cool the reaction mixture to room temperature and dilute with dichloromethane. Pour the reaction mixture into water and separate the organic layer. Extract the aqueous layer with dichloromethane (10 mL). Wash the combined extracts with water and dry over anhydrous magnesium sulfate. Evaporate the solvent under vacuum give a solid, and treat the solid with ethyl acetate. Remove the solid by filtration and wash the solid with ethyl acetate. Evaporate the filtrate under vacuum to give a semisolid residue. Dissolve the residue in DMSO (1 mL) and apply the solution onto a column of silica gel (46 g.). Elute the column with the ethyl acetate-hexanes (3:2, v/v). Evaporate the eluant and isolate four compounds: phthalimide, unreacted starting material (26.0 mg.), unknown component A (24.6 mg.), and component B (104 mg.). The component B contained two to three compounds including the title compound (50%). Dissolve a portion (80 mg.) of this mixture (compound B) in hot isopropyl alcohol (3 mL) and cool the solution to room temperature and thence to 0°. A crystalline solid was removed by filtration and washed with cold isopropyl alcohol (22 mg., 15%). The compound had m.p., and ir and ^{1}H NMR spectra, identical to those, respectively, of the title compound obtained in procedure (A) of Example 4.

EXAMPLE 5

D,L-(threo)-1-(4-Methylsulfonylphenyl)-2-Amino-3-Fluoro-1-Propanol

Dissolve hydroxylamine hydrochloride (460 mg.) in dry methanol (25 mL) (dried with Mg) with stirring. Add solid sodium methoxide (575 mg.) to the resulting solution and stir the mixture for 0.5 hr. Remove the precipitated solid by suction filtration. To the clear filtrate, add the title compound of Example 4 (500 mg., 1.32 mmoles). Stir the mixture for 19 hrs. at room temperature. Evaporate the solvent under vacuum and stir the resulting syrupy residue with an ice-cooled mixture of chloroform (10 mL), 30% NaOH solution (10 mL) and methanol (2 mL) until the residue completely dissolves. Separate the organic layer and extract the aqueous layer with chloroform (5 x 10 mL). Dry the combined chloroform extracts over anhydrous Na_2SO_4 and evaporate the solvent under vacuum to give a syrup which crystallized spontaneously (yield 381 mg. 97%). Recrystallize from methanol to give the title compound, white crystals; m.p. 143-144°, R_f = 0.22 (solvent C), ν_{max} (KBr): 3330 and 3270 (NH_2), 3040 (OH), 1581 (NH_2) cm^{-1}; ^1H NMR ($CDCl_3$-DMSO-d_6, 2:1, v/v) δ:1.46 (NH_2) (bs, 2H), 2.97-3.12 (m, 1H), 3.07 (s, 3H), 4.18 (ddd, 1H, $J_{3,F}$ = 34.2 Hz, $J_{3,3'}$ = 9.0 Hz, $J_{3,2}$ = 5.9 Hz), 4.41 (ddd, 1H, $J_{3',F}$ = 34.2 Hz, $J_{3',3}$ = 9 Hz, $J_{3',2}$ = 5.9 Hz), 4.71 (d, 1H, $J_{1,2}$ = 4.2 Hz), 5.53 (OH) (bs, 1H), 7.53 (d, 2H, J = 8.1 Hz), 7.80 (d, 2H, J = 8.1 Hz).

EXAMPLE 6

D,L-(threo)-1-(4-Methylsulfonylphenyl-2-Azido-3-Fluoro-1-Propanol

Heat a mixture of the title compound of Example 3 (500 mg., 2.17 mmoles), sodium azide (565 mg.), and ammonium chloride (465 mg) in dry DMSO (10 mL), with

stirring, in an oil bath at 70° for 12 hrs. Pour the resulting reaction mixture into ice water and extract twice with dichloromethane (30 mL x 2). Wash the combined extracts with water twice and dry the washed extracts over anhydrous sodium sulfate. Evaporate the solvent to give a syrup (491 mg.) and dissolve the resulting syrup with a small amount of dichloromethane. Add ether to the resulting solution. Collect a crystalline solid by filtration and wash it with ether to give the title compound (yield 164 mg., 27.6%);

m.p. 121-123°, R_f = 0.33 (solvent B); ν_{max} (KBr):3430 (OH), 2990, 2080 (N_3), 1585 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$-DMSO-d_6, 4:1, v/v),δ:3.07 (s, 3H), 3.75 (m, 1H, $J_{2,1}$ = 5.2 Hz, $J_{2,3}$ = 6.8 Hz, $J_{2,3'}$ = 3.6 Hz, $J_{2,F}$ = 18.2 Hz), 4.31 (ddd, 1H, $J_{3,F}$ = 47.5 Hz, $J_{3,2}$ = 6.8 Hz, $J_{3,3'}$ = 10.0 Hz), 4.61 (ddd, 1H, $J_{3',F}$ = 45.3 Hz, $J_{3',2}$ = 3.6 Hz, $J_{3,3'}$ = 10.0 Hz), 4.90 (t, 1H, $J_{1,2}$ = $J_{1,OH}$ = 5.2 Hz), 5.94 (OH) (d,1H, $J_{OH,1}$ = 5.2 Hz), 7.59 (d, 2H, J = 8.1 Hz), 7.85 (d, 2H, J = 8.1 Hz).

EXAMPLE 7

D,L-(threo)-1-(4-Methylsulfonylphenyl)-2-Amino-3-Fluoro-1-Propanol

Dissolve the title compound of Example 6 (100 mg.) in methanol (25 mL) and add 10% palladium-on-charcoal (16 mg.) in methanol (2-3 mL) to the solution. Shake the resulting mixture in a Parr apparatus under hydrogen at atmospheric pressure at room temperature for 1.5 hr. Remove catalyst by filtration and wash same with methanol. Evaporate solvent under vacuum to afford the title compound as a syrup (~ 90 mg.). The compound was essentially homogeneous on tlc, and was used in Example 8B without purification.

EXAMPLE 8

D,L-(threo)-1-(4-Methylsulfonylphenyl)-2-Dichloro-Acetamido-3-Fluoro-1-Propanol

A. Dissolve the title compound of Example 5 (208 mg., 0.841 mmoles) in methyl dichloroacetate (4 mL), triethylamine (0.1 mL) and dry methanol (1.6 mL). Reflux the resulting solution for 11 hrs. under nitrogen. Evaporate solvent under vacuum (0.5 mmHg) to give a syrup. Dissolve the syrup in dichloromethane and apply the resulting solution on to a column of silica gel (45 g.). Elute the column with ethyl acetate-hexanes (4:1, v/v) to give a solid 22 mg., 82%). Recrystallize the solid from a small amount of isopropyl alcohol and ether to give the title compound, white, fine crystals; m.p. 150-151.5° (cf. D-(threo)-isomer; m.p. 151.5-152°), R_f = 0.48 (solvent D); ν_{max} (KBr): 3450 (OH), 3300 (NH), 1669 (C=O), 1583 (C=C), 1511 (NH); ^1H NMR ($CDCl_3$-DMSO-d_6, 4:1, v/v), δ: 3.02 (s,3H), 4.23-4.51 (m, 2H, H_2 and H_3), 4.60 (ddd, 1H, $J_{3',F}$ = 40.3 Hz, $J_{3',2}$ = 7.2 Hz, $J_{3,3'}$ = 8.9 Hz), 5.03 (dd, 1H, $J_{1,OH}$ = 5.0 Hz, $J_{1,2}$ = 1.4 Hz), 5.91 (OH) (d, 1H, $J_{OH,1}$ = 5.0 Hz), 6.17 ($CHCl_2$) (s,1H), 7.58 (d, 2H, 8.4 Hz), 8.19 (d, 2H, 8.5 Hz).

B. Dissolve the title compound of Example 7 (90 mg., 0.36 mmoles) in dry methanol (Mg. dried, 1.6 mL), triethylamine (0.1 mL) and methyl dichloroacetate (4 mL). Reflux the solution under nitrogen for 14 hrs. Evaporate solvent under vacuum to give a syrup. Chromatograph the syrup on a silica gel column, elute with ethyl acetate-hexanes (3:1, v/v) to give a solid after evaporation of the solvent (yield, 102 mg., 86.8%). Recrystallize the solid from isopropyl alcohol and ether to give the title compound as fine, white crystals, m.p. 148-149° and having identical ir and

^{1}H NMR spectra with those, respectively, of the dichloroacetamido derivative prepared from the phthalimide in accordance with procedure A of Example 8.

EXAMPLE 9

D-(threo)-(4-Methylsulfonylphenyl)-2-Amino-3-Fluoro-1-Propanol by resolution of D,L-(threo)1-(4-Methylsulfonylphenyl)-2-Amino-3-Fluoro-1-Propanol

A. Resolution of (+)-(S)-O-methylmanclelic acid,. Heat 40.0 g. (0.241 moles) of racemic (±)-α-methyl-α-phenylacetic acid [D.G. Neilson et al. J. Chem. Soc., (1962), 1519] with 40.0 g. (0.242 moles) of d-ephedrine (available from Aldrich) in 180 mL of 95% ethanol under reflux on a steam bath. Cool the resulting solution to room temperature slowly and leave undisturbed overnight (16 hrs.). Filter the resulting crystallized solid and wash same with 95% ethanol (20 mL) and ethyl ether to give 35.6 g. Recrystallize (twice) the solid from 95% ethanol to give 26.5 g. of salt of d-ephedrine and (+)-α-methoxy-α-phenylacetic acid [(+)-(S)-O-methylmandelic acid], m.p. 185-188°, $[\alpha]_D^{21}$ + 72.8° (c, 4.64, MeOH). Acidify 26.3 g. of the solid with 90 mL of ice-cooled sulfuric acid, with stirring to give a solution. Add sodium chloride (31 g.) and stir the resulting mixture. Add 100 mL of dichloromethane to the mixture to give a voluminous precipitate (ephedrine, sulfuric acid salt). Add another 100 mL portion of dichloromethane to the mixture and filter the mixture through a glass filter. Wash the solid with 100 mL of dichloromethane. Shake the filtrate and separate the organic and aqueous layers. Extract the aqueous layer with 100 ml of dichloromethane. Dry the combined organic layers over anhydrous magnesium sulfate. Evaporate the solvent to give an oil which solidifies on cooling to yield 13.2 g. of the title compound as a solid: m.p. 60.5-62.0°, $[\alpha]_D^{22}$ + 149° (C, 5.61, MeOH).

B. Formation of seed crystals of the salt of (+)-(S)-O-Methylmandelic acid and D-(threo)-1-(4-Methylsulfonylphenyl)-2-Smino-3-Fluoro-1-Propanol.

Dissolve (+)-(S)-O-Methylmandelic acid from Example 9, procedure A (44.9 mg., 0.270 mmole) and authentic D-threo-1-(4-methanesulfonylphenyl)-2-amino-3-fluoro-1-propanol (obtained by hydrolysis of the corresponding 2-dichloroacetamido derivative prepared in accordance with USP 4,311,857 using 33% HCl solution followed by treatment with 30% NaOH solution and extraction of the free base) (66.9 mg., 0.270 mmole) in n-butanol (1.5 mL) by warming on a steam bath. Cool the solution slowly to room temperature and leave the cooled solution undisturbed for 15 hrs. Filter the crystalline solid by filtration and wash the solid with an ether - n-butanol mixture (1:1, v/v) 2 mL) and ether (yield 84 mg.). Recrystallization gave fine needles of the title salt, m.p. 160-161.5°, $[\alpha]_D^{23}$ + 22.7° (c 11.8, MeOH); ν_{max} (KBr): 3400, 3190, 2870, 2700, 2540, 1560, 1400, 1302 cm^{-1}.

C. Condition 1: Crystallizing the diastereomeric salt with stirring.

Dissolve D,L-(threo)-1-(4-methylsulfonylphenyl)-2-amino-3-fluoro-1-propanol of Example 8 (1.193 g., 4.822 mmoles) and (+)-(S)-O-methylmandelic acid (0.8012 g, 4.822 mmoles) of Example 9A in n-butanol (25 mL) by warming on a steam bath. While the resulting solution is cooling to room temperature, seed the warm solution with an authentic sample of the salt (2 mg.) described in procedure (B) Example 9. Stir the mixture rigorously for 2 hrs. at room temperature. Remove the precipitated solid by filtration and wash the solid with an ice-cooled (1:1, v/v) n-butanol - anhydrous ether mixture (10 mL)

mL) on a steam bath. Cool the solution to room temperature, and seed the turbid solution with the authentic salt described in procedure B of Example 9 and leave the seeded solution at room temperature without disturbance for 65 hrs. Collect the crystalline solid by filtration and wash the collected solid with an n-butanol and ether mixture (1:1, v/v) (10 mL) and ether (45 mL), and finally dry under vacuum, yield 1.4289 g.; $[\alpha]_D^{21.9}$ + 35.9° (c 9.03, MeOH). Recrystallize the partially enriched solid (1.375 g.) from n-butanol (15 mL) as described above except leave same at room temperature for 24 hrs., yield 0.005 g.; $[\alpha]_D^{22.4}$ + 31.7° (c 8.80, MeOH).

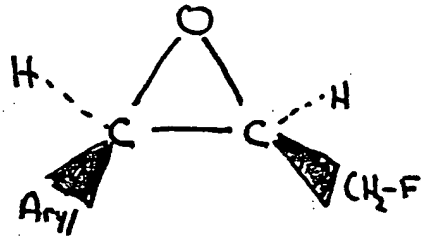
Recrystallize this solid (0.9118 g.) from n-butanol (10 mL) as described above to give a solid (yield 0.6951 g.), $[\alpha]_D^{22.2}$ + 28.3° (c 9.00, MeOH). Recrystallize this material (0.6349 g.) from n-butanol (5 mL) to afford a solid (yield 0.5046 g.). $[\alpha]_D^{23.8}$ + 26.4° (c 10.3, MeOH). Recrystallize the major portion of this solid (0.4433 g.) from n-butanol (4 mL) to give a solid (yield 0.2325 g.), m.p. 159-161.5°, $[\alpha]_D^{23.0}$ + 24.2° (c 9.95, MeOH). Decompose this salt (0.1800 g.) using sodium hydroxide solution as described in procedure B of this Example and isolate the title compound (yield 0.1013 g., 94.1%); $[\alpha]_D^{23.0}$ - 32° (c 1.95, MeOH) cf. authentic sample of the title compound of this Example, $[\alpha]_D^{22}$ - 35° (c 2.03, MeOH . Optical purity %: -32°/-35° x 100 = 91%.

Racemic mixtures of the following D,L-(threo)-1-Aryl-2-amino-3-fluoro-1-propanols may be prepared using the appropriate reagents and thereafter resolved by fractional crystallization of their diastereomeric salts with the appropriate optically active acid in accordance with the procedures detailed hereinabove as well as the prior teachings of S.H. Wilen, in "Topics in Stereochemistry" ed by N.L. Allinger and E.L. Eliel, Vol. 6, p. 107 et seq., Wiley-Interscience, New York, 1971 and R.B. Woodward et al., Tetrahedron, Vol. 19 (1963) page 247 et seq.f157

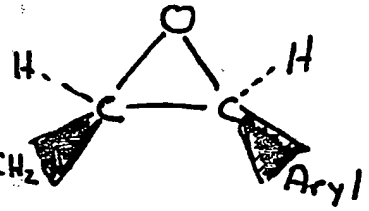
CLAIMS

What is claimed is:

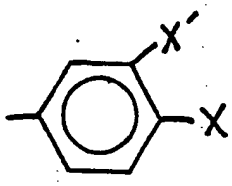
1. A process for preparation of compounds represented by formulas IVa and IVb:



IVa



IVb

wherein Aryl is  ; and

wherein each of X and X' is independently NO_2, SO_2R_1, SO_2NHR_1, OR_1, R_1, CN, halogen, hydrogen, phenyl, or phenyl substituted by 1-3 halogens, NO_2, SO_2R_1, R_1 or OR_1; and wherein R_1 is lower alkyl; which comprises contacting a cis-1-Aryl-3-fluoro-1-propane with a peroxyacid to form the compounds represented by the formulas IVa and IVb.

2. The process of claim 1 wherein Aryl is selected from 4-methylsulfonylphenyl, 4-nitrophenyl and 4-sulfonamidophenyl.

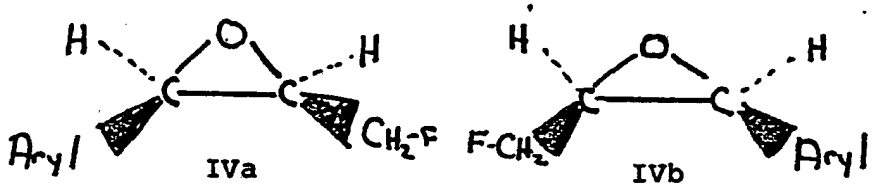
3. The process of claim 1 or 2 wherein the cis-1-Aryl-3-fluoro-1-propene is prepared by

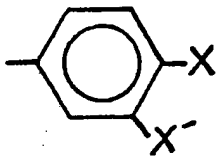
a) contacting a 3-Aryl-2-propyn-1-ol with a fluorinating agent in an inert organic solvent to form 1-Aryl-3-fluoro-1-propyne; and

b) contacting the product of step (a) with a reagent selective for cis-hydrogenation

wherein Aryl is as defined in claim 1.

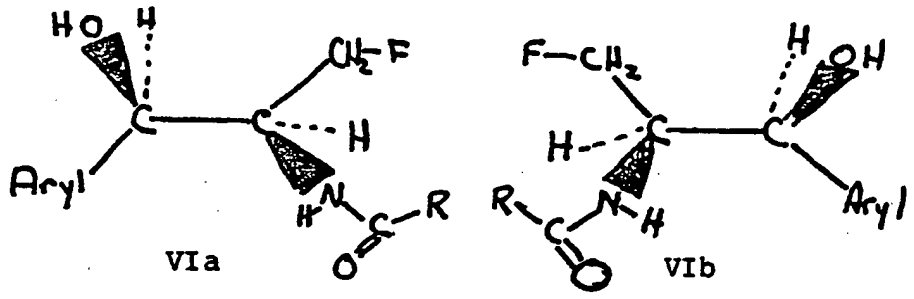
4. A compound represented by the formulas IVa and IVb:



wherein Aryl is  ; and wherein each of X and X' is independently NO_2, SO_2R_1, SO_2NH_2, SO_2NHR_1, OR_1, R_1, CN, halogen, hydrogen, phenyl or phenyl substituted by 1 to 3 halogens, NO_2, SO_2R_1, R_1 or OR_1; and wherein R_1 is lower alkyl.

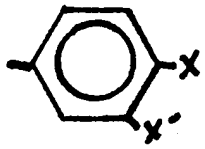
5. The compound of claim 4 wherein Aryl is selected from 4-nitrophenyl, 4-sulfonamidophenyl and 4-methylsulfonylphenyl.

6. A process for the preparation of D,L-(threo)-1-Aryl-2-acylamido-3-fluoro-1-propanol represented by the formulas VIa and VIb:



VIa VIb

wherein R is lower alkyl or a halogenated derivative thereof, dihalogeneodeuteriomethyl, 1-halogeno-1-deuterioethyl, 1,2-dihalogeno-1-deuterioethyl, azidomethyl and methylsulfonyl;

wherein Aryl is  ; and wherein each of X and X' is independently NO_2, SO_2R_1, SO_2NH_2, SO_2NHR_1, OR_1, R_1,CN, halogen, hydrogen, phenyl or phenyl substituted by 1 to 3 halogens, NO_2, SO_2R_1, R_1 or OR_1; and wherein R_1 is lower alkyl; which comprises the following steps:

(1) converting a cis-1-Aryl-2-(fluoromethyl)oxirane into D,L-(threo)-1-Aryl-2-amino-3-fluoro-1-propanol either by (i) contacting the cis-1-Aryl-2-(fluoromethyl)oxirane with an alkali metal azide to form D,L-(threo)-1-Aryl-2-azido-3-fluoro-1-propanol and then reducing the 2-azido group to the 2-amino group or (ii) contacting the cis-1-Aryl-2-(fluoromethyl)oxirane with an imido compound to form a D,L-(threo)-1-Aryl-2-imido-3-fluoro-1-propanol and then converting the 2-imido group to a 2-amino group thereby forming D,L-(threo)-1-Aryl-2-amino-3-fluoro-1-propanol;

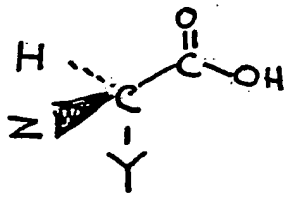
(2) contacting the product of step (1) with a lower alkanoic acid derivative selected from lower alkyl alkanoic acid anhydrides, lower alkyl alkanoyl halides, a lower alkyl halogeno alkanoic halide or anhydride in the presence of base, or with lower alkyl ester of an α,α-dihalogeno acetic acid or of an α,α-dihalogeno propionic acid ester in a lower alkanol to produce the compounds of formulas VIa and VIb; and

(3) recovering the compounds of formulas VIa and VIb.

7. The process of claim 6 which further comprises recovering D-(threo)-1-Aryl-2-amino-3-fluoro-1-propanol represented by formula Va from fractional crystallization of diastereomeric salts of compounds represented by formulas Va and Vb and an optically active acid; and thence performing step (2).

8. The process of claim 6 wherein Aryl is selected from 4-methylsulfonylphenyl, 4-nitrophenyl and 4-sulfonamidephenyl.

9. The process of claim 7 wherein the optically active acid has the structure represented by formula A:



A

wherein Z is a bulky group and wherein Y is a polar group.

10. The process of claim 7 wherein Aryl is 4-methylsulfonylphenyl and wherein, in the optically active acid, Z is phenyl or naphthyl and Y is (C_1-C_6)alkyloxy.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 85/01753

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[4]: C 07 D 301/14; C 07 D 303/34; C 07 C 147/06; C 07 B 43/00// C 07 D 209/48; C 07 B 57/00

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[4]	C 07 D 301/00; C 07 D 303/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
A	Bulletin de la Société Chimique de France, volume 12, 1945, Paris (FR) J.P. Fourneau et al.: "Recherches sur les amino-acétals", pages 845-864, see page 854, 4th formula and page 855, lines 13-20 --	1-5
A	DD, A, 83161 (RUDOLF KREBS) 12 July 1971, see claim 1 --	1-10
A	GB, A, 2025417 (CONTINENTAL PHARMA) 23 January 1980, see page 5, example 2 --	1-10
A	EP, A, 0014437 (SCHERING CORPORATION) 20 August 1980, see claim 1 (cited in the application)	1-10

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* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
16th December 1985	16 JAN. 1986
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	G.L.M. Kruydenberg

Form PCT/ISA/210 (second sheet) (January 1985)

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON

INTERNATIONAL APPLICATION NO. PCT/US 85/01753 (SA 10667)

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 08/01/86

The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
DD-A- 83161		None		
GB-A- 2025417	23/01/80	BE-A-	877694	05/11/79
		NL-A-	7905507	15/01/80
		DE-A-	2927789	24/01/80
		LU-A-	79970	14/02/80
		FR-A,B	2438649	09/05/80
		FR-A,B	2443457	04/07/80
		JP-A-	55033467	08/03/80
		CA-A-	1127164	06/07/82
		AT-B-	368491	11/10/82
		AT-B-	371106	10/06/83
		AT-B-	371107	10/06/83
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		AU-A-	5507880	10/07/80
		JP-A-	55115855	06/09/80
		US-A-	4311857	19/01/82
		CA-A-	1137106	07/12/82
		AT-B-	E2616	15/03/83
		AU-B-	532879	20/10/83